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## **CliniMACS Prodigy™ - Tubing sets and Sterile Filter Integrity Regulatory Guidelines**

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### **The Challenge**

The challenge was to address a regulatory concern regarding post use integrity testing of filters integral to Miltenyi Biotec's CliniMACS Prodigy™ tubesets used for ATMP production in both clinical and commercial settings. Due to an update in interpretation of the Pre-use Post Sterilisation Integrity Testing (PUPSIT) regulatory guidelines, NA-ATCC partners requested a protocol to allow post use integrity testing to be performed to allow local testing and ensure regulatory compliance by demonstrating integrity of the filters within the tubeset.

### **The Solution**

Details of the PUPSIT expectations and the optimum solution were provided to Regulatory affairs (RA) at Miltenyi Biotec who subsequently communicated all testing procedures used for CliniMACS Prodigy™ tubing set allowing local testing to be performed. These tests demonstrating maintenance of the closed system and that the filters would retain any bacterial contamination, as such complying with the PUPSIT regulatory expectations. These test parameters were trialled within the NA-ATTC supported by Miltenyi Biotec, who subsequently used this real world application to produce a procedure and guidance for integrity testing of the CliniMACS Prodigy™ tubing sets filters.

### **The Results**

Information provided by Miltenyi Biotec in response to NA-ATTC partner questions produced a clear process for manufacturers to follow. Discussions led to the development and release of the attached SOPs:

- **Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets**
- **Protocol for post use integrity test of hydrophobic filters as components of CliniMACS Prodigy Tubing Sets**

With thanks to contributing NA-ATTC partners; Miltenyi Biotec, Autolus, SNBTS, Newcastle Advanced Therapies and The Newcastle upon Tyne Hospitals NHS Foundation Trust.

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# Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets



## CAUTION:

- To reduce the risk associated with exposure to infectious or otherwise harming residuals inside the used tubing set always use appropriate personal protective equipment and technical environment when de-connecting and handling the filters.
- Integrity testing devices release high pressure. Please consult Instructions for Use of the used integrity testing device.

## 1 Purpose

This protocol describes the materials, limit values and procedures required to perform a bubble point test of hydrophilic media filters, reagent filters and cytokine filters.

## 2 Scope

This document provides a guide for customers using the CliniMACS Prodigy System to support a filter integrity test of hydrophilic filters that are part of the CliniMACS Prodigy Tubing Set and Accessories family, as shown in the following figure:

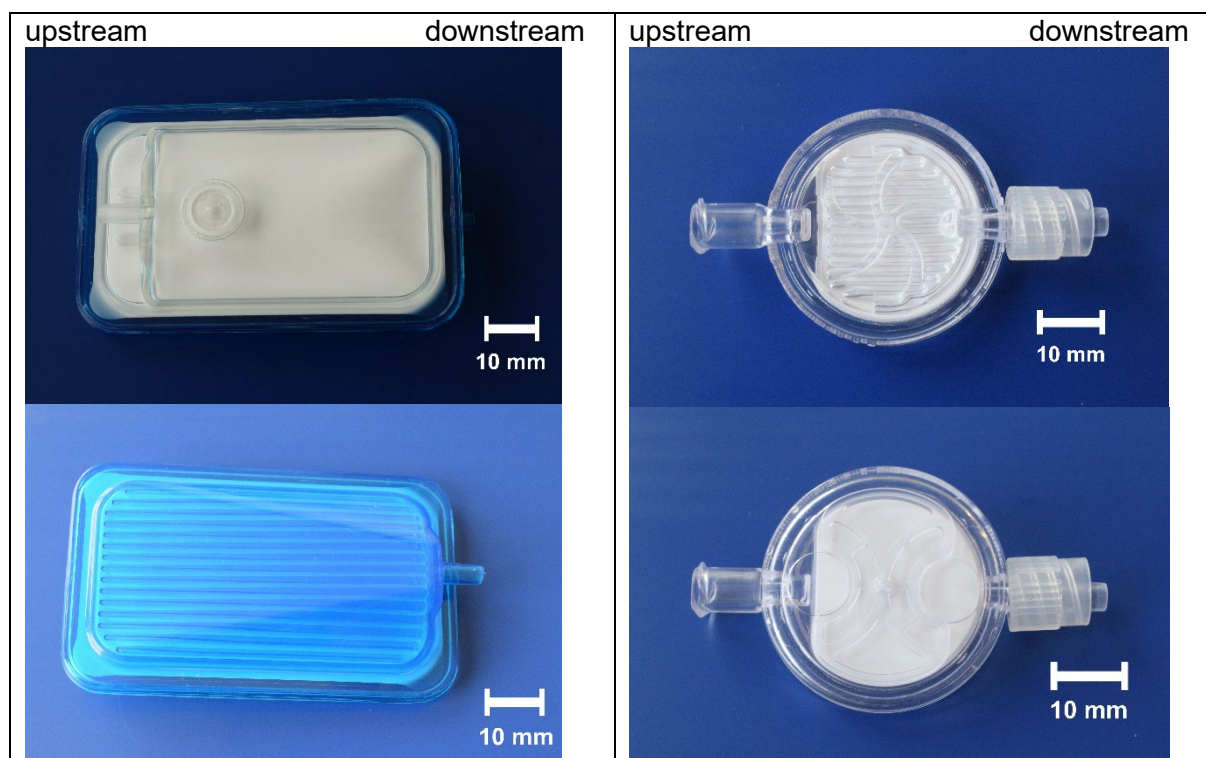


Figure 1: Hydrophilic filters used in CliniMACS Prodigy Tubing Sets: media filter (left) and reagent filter (right).

## Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets

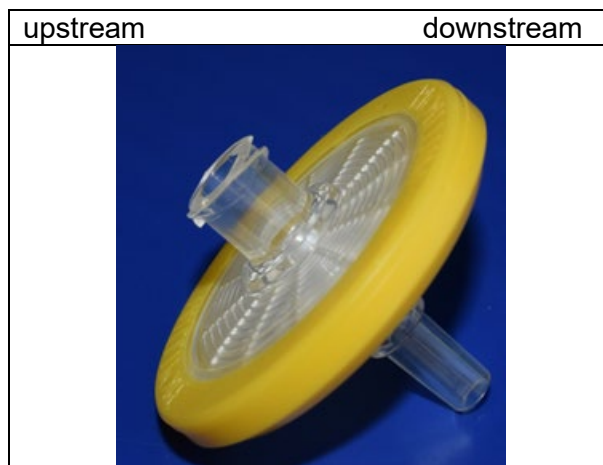


Figure 2: Hydrophilic filter used in CliniMACS Prodigy Accessory Cytokine Vial Adapter

### 3 Abbreviations

BP  
min  
bar

Bubble Point  
Minutes  
Unit of pressure

### 4 Responsibilities

Everyone, who performs a filter integrity test, shall observe this procedure first.

### 5 Materials and equipment

- Filters to be tested
- Mechanism to block air vent of media filters (test fixture for single filter (REF 150-001-912; test fixture for triple filter assembly (REF 150-001-911)
- 50 ml syringe
- Wetting medium (tap water)
- Luer lock adapters (male-male, female-female)
- Compressed air with pressure reducer (3-8 bar)
- Filter integrity test device including female Luer connector (e.g. Palltronic Flowstar, Integritest® 4N Integrity Test, Instrument Millipore, Sartocheck)

## 6 Procedure

### 6.1 General Notes

- The filter integrity test is performed at room temperature.
- Always avoid temperature drift during the test, e.g. due to not adjusting the temperature of the wetting medium (tap water) (gas temperature = temperature of the wetting medium (tap water) = room temperature).
- Holding time (time between usage of tubing set and execution of filter integrity test) is maximum 24 hours

*Note: When defining the measuring range, do not exceed 4 bar of maximum pressure during the test.*

The minimum BPs for the filters (provided by manufacturer) are:

Media filter	3100 mbar
Reagent filter	3200 mbar
Cytokine filter	3450 mbar

### 6.2 Preparation for Filter Testing

#### 6.2.1 Disconnecting the filters from the tubing set after use:

- Weld off the filters from tubing set before deinstallation.
- Make sure that the tubing at the downstream side of the filter is as long as possible.
- Make sure that a Luer connector is available at the upstream side of the filter(s).
- If possible, close the upstream side with a clamp.
- Unscrew the vial adapters or spike ports.

## Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets

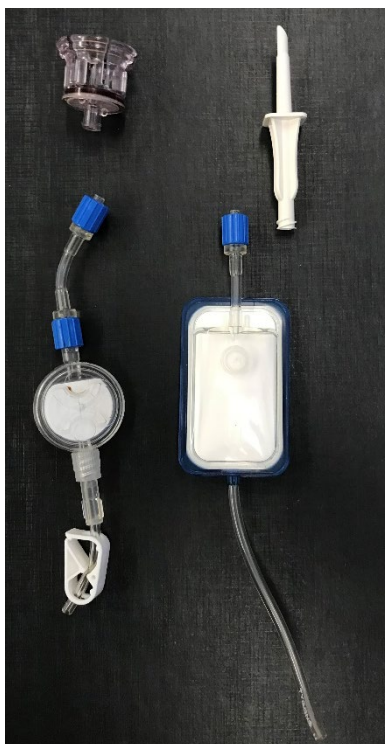


Figure 3: Prepared hydrophilic filters for flushing. Media filter (right) and reagent filter (left) are pointing downwards with their downstream tubing. During the test the device is connected to the upper part / upstream side of the filter (blue Luer Locks)

### Flushing of the filter

- Media filter assemblies
  - Fill a 50 ml syringe with wetting medium (tap water) at room temperature.
  - Connect the syringe to the upstream side of the filter(s) via Luer. Use a female-female Luer Lock adapter, if necessary.
  - Make sure that the (welded-off) tube at the downstream side of the filter(s) is open.
  - Make sure that the air-vents of the filter(s) is / are open.
  - Make sure that the filter(s) is / are positioned in a vertical position with the upstream side facing upwards.
  - After opening the clamps at the up- and downstream side rinse the filter(s) carefully with at least 50 ml of wetting medium (tap water). Make sure not to introduce air into the filter.
  - Close the tube on both the down- and upstream side with a clamp.
  - Remove the syringe from the filter.

## Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets



### Reagent filter

- Connect an empty 50 ml syringe to the upstream side of the filter via Luer. Use a female-female Luer Lock adapter, if necessary.
- Make sure that the filter is positioned in a vertical position with the upstream side facing up.
- Make sure that the (welded-off) tube at the downstream side of the filter is open.
- Hold the tube at the downstream side into a vessel filled with wetting medium (tap water) at room temperature.
- After opening the clamps at the up- and downstream side gently pull the piston upwards to fill up the syringe with 5 to 10 ml of wetting medium (tap water). This will flush the filter in reverse direction.

*Note: Wrong or too fast rinsing of the filter can damage the filter delivering incorrect results during the integrity test.*

- Close the tube on both the down- and upstream side with a clamp.
- Remove the syringe from the upstream side of the filter and fill the syringe with 50 ml of wetting medium (tap water).
- Reconnect the syringe to the upstream side via Luer.
- Remove the clamp at the tube at the downstream side and carefully rinse the filter downstream. Make sure not to introduce air into the filter.
- Close the tube at the downstream side with a clamp and remove the syringe from the upstream side of the filter.
- Cytokine filter
  - Fill a 50 ml syringe with wetting medium (tap water) at room temperature.
  - Open the upstream side of the filter and connect the syringe via Luer. Use a male-male Luer Lock adapter, if necessary.
  - Make sure that the (welded-off) tube at the downstream side of the filter(s) is open.
  - Make sure that the filter is positioned in a vertical position with the upstream side facing upwards.
  - Rinse the filter(s) carefully with at least 20 ml of wetting medium (tap water).
  - Close the tube on the downstream side with a clamp.
  - Remove the syringe from the filter.

**Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets**



6.2.2 Closing the air-vent on media filter assemblies by the test fixtures

- Triple filter assembly:

<p>De-connected media filter (triple assembly) and spacers of test fixture:</p> <ul style="list-style-type: none"> <li>• The air vent of the media filter is located at the side opening of the filter housing.</li> <li>• The sealing ring closes the air vent opening of the filter.</li> </ul>	
<ul style="list-style-type: none"> <li>• The air vent opening (see marked area) is placed onto the sealing dome located in the base of the mechanism (see marked area in the next step).</li> <li>• After insertion into the mechanism the upstream side is pointing to the right and the blue side of the filter housing faces up</li> </ul>	
<p>Test fixture for preparation of the media filter for integrity testing:</p> <ul style="list-style-type: none"> <li>• Prepare the filter assembly by inserting it in the test fixture</li> <li>• For placement of the spacers see instructions in the next step</li> </ul> <p><i>Note: The respective mechanism for the Triple Filter Assembly has to be used.</i></p>	

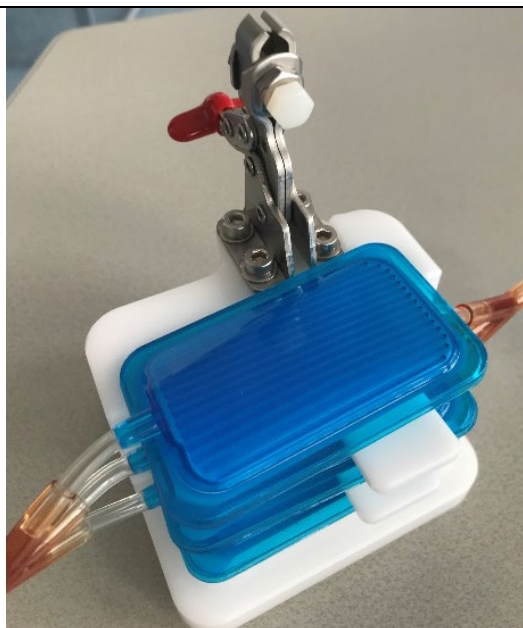
## Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets



- Turn the filter assembly so that the blue side of the filter housing faces up.
- Place the spacers of the test fixture between the filter housings and close the test fixture with the red lever, while holding the filters in place.

*Note: If triple filter assembly does not fit in the test fixture, preparation has not been done correctly.*

- The filters are now ready to be tested.



- Single filter assembly:
  - Note: General handling steps are similar to steps for preparation of the triple filter assembly.*
  - The air vent opening is placed onto the sealing dome located in the base of the test fixture.
  - Make sure that the sealing ring around the dome sits flush and even against the filter housing.
  - Place the silicone barrier of the test fixture on the filter housing and close the test fixture with the red lever, while holding the filter in place.
  - The filter is now ready to be tested.



## Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets



Single filter assembly prepared for filter integrity testing by use of test fixture:



### 6.2.3 Filter testing

- Connect the Luer connector at the upstream side of the filter to the pressure outlet of the bubble point test device. To test the cytokine filter, use a male-male Luer adapter or the corresponding male Luer connector of your test device.

*Note: The upstream filter system has to be absolutely leakproof.*

- Make sure that available air vents of the media filter(s) have been closed beforehand.
- Select the appropriate program.
- Open both, the down- and upstream side of the filter.
- Start the test program according to the corresponding setup and use the handling instructions of the device.

*Note: Vent the filtration system housing immediately after each test to avoid contamination of the integrity tester!*

- Vent the filter completely and disconnect the filter from the pressure outlet.
- Air vents of media filters are not to be tested for integrity.

## 7 Example results for bubble point measurements

After the measurement is finished, the filter integrity test device will provide a printout summarizing the program parameters, the results of the test in a tabular and graphic form and whether the test was passed or not. In addition, the figures below serve as a reference to the resulting data.

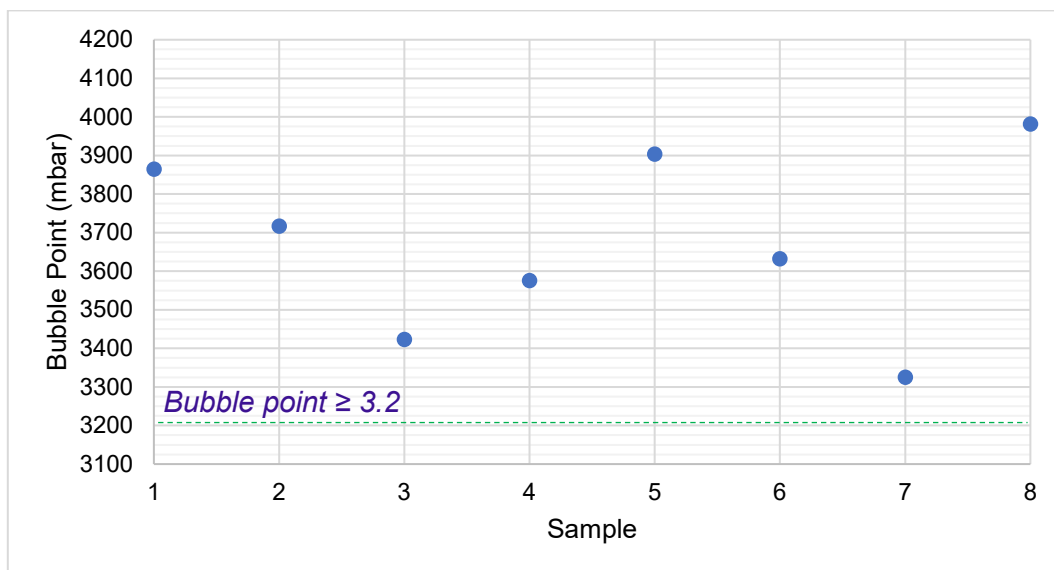


Figure 4: Example - bubble point test of hydrophilic filter – reagent filter

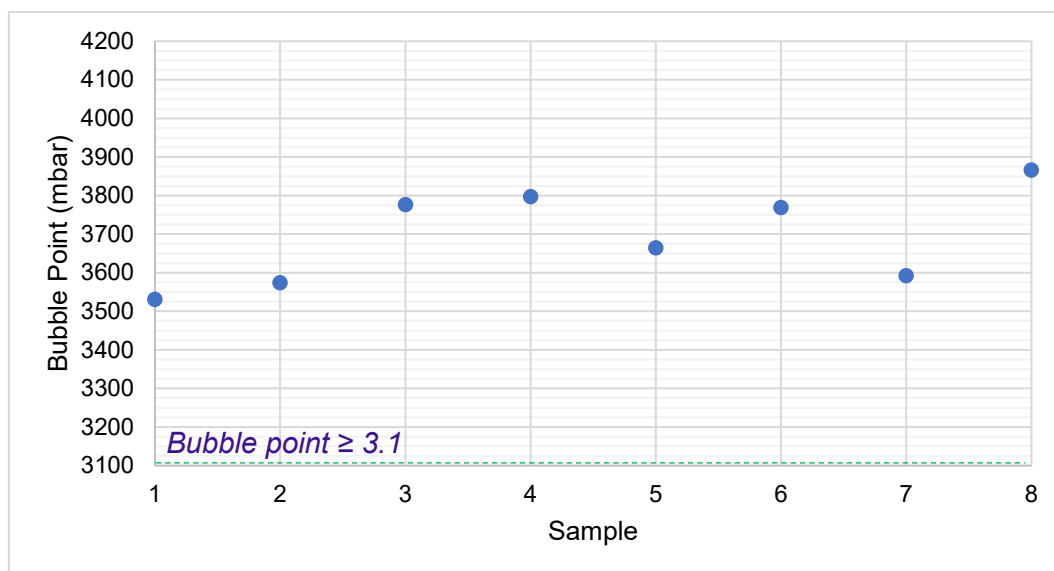


Figure 5: Example - bubble point test of hydrophilic filter - media filter

Protocol for post use integrity test of hydrophilic filters as components of CliniMACS Prodigy Tubing Sets

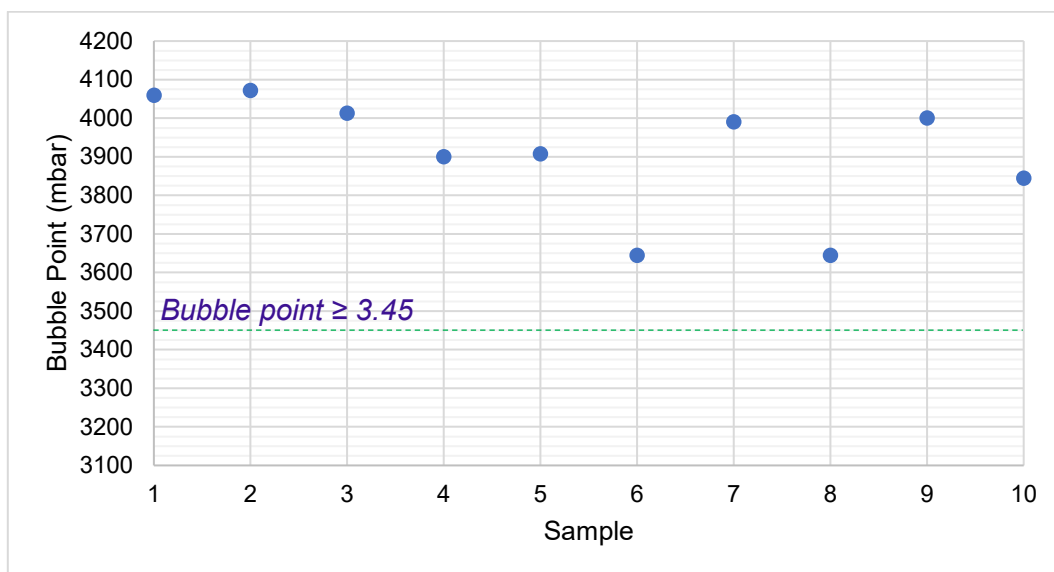


Figure 6: Example - bubble point test of hydrophilic filter - cytokine filter

# Protocol for post use integrity test of hydrophobic filters as components of CliniMACS Prodigy Tubing Sets



## CAUTION:

- To reduce the risk associated with exposure to infectious or otherwise harming residuals inside the used tubing set always use appropriate personal protective equipment and technical environment when de-connecting and handling the filters.
- Integrity testing devices release high pressure. Please consult Instructions for Use of the used device.

## 1 Purpose

This protocol describes the materials, limit values and procedures required to perform a water intrusion test of hydrophobic filter units.

## 2 Scope

This document is provided as a guide for customers using the CliniMACS Prodigy System to support a filter integrity test of hydrophobic filters that are part of the CliniMACS Prodigy tubing set family, as shown in the following figure:

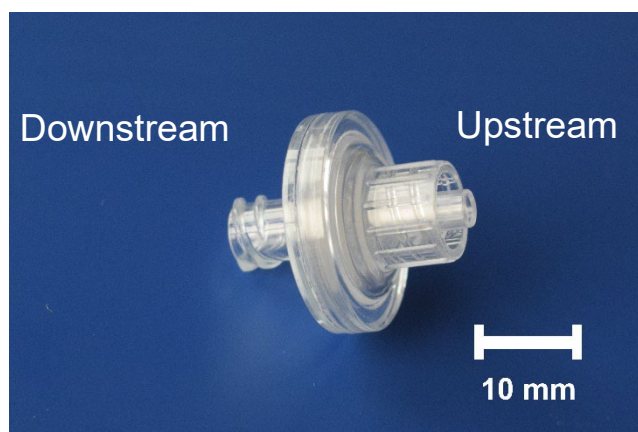


Figure 1: Hydrophobic air filter used in CliniMACS Prodigy Tubing Sets

# Protocol for post use integrity test of hydrophobic filters as components of CliniMACS Prodigy Tubing Sets



## 3 Abbreviations

min	Minutes
bar	Unit of pressure
WIT	Water Intrusion Test

## 4 Responsibilities

Everyone, who performs a filter integrity test, shall observe this procedure first.

## 5 Materials and equipment

- Filters to be tested
- Compressed air with pressure reducer (3-8 bar)
- Filter integrity test device including female Luer connector (e.g. Palltronic Flowstar, Integritest® 4N Integrity Test, Instrument Millipore, Sartocheck)

## 6 Procedure

### 6.1 General notes

- Holding time (time between usage of tubing set and execution of filter integrity test) is maximum 24 hours
- The filter integrity test is performed at room temperature.
- Always avoid temperature drift during the test, e.g. due to not adjusting the temperature of the wetting medium (tap water) (gas temperature = temperature of the wetting medium (tap water) = room temperature).
- Make sure that the surface tension of the wetting medium (tap water) used is > 70 dyn/cm.

*Note: It is recommended to use water or dH<sub>2</sub>O at a maximum temperature of 25 °C.*

- Use the settings shown in Table 1 for the filter.

#### 6.1.1 Program parameters for the water intrusion test

Table 1: Program parameters for the water intrusion test (Water flow)

Parameter	Value
Test Pressure (mbar)	3200
Stabil. Time 1 (min)	3
Stabil. Time 2 (min)	3
Test Time (min)	3

## Protocol for post use integrity test of hydrophobic filters as components of CliniMACS Prodigy Tubing Sets



### 6.2 Preparation for filter testing

#### 6.2.1 Disconnecting the filters from the tubing set after use:

- Weld-off the filters from the tubing set at their upstream side before deinstallation.
- Make sure that the Luer connector is available at the upstream side of the filter.
- If possible, close the downstream side with a Luer cap. (The Luer cap that is being removed during tubing set installation can be used).

### 6.3 Water intrusion measurement

#### 6.3.1 Flushing of filter

- Fill a syringe with wetting medium (tap water) at room temperature.
- Connect the syringe to the Luer lock at the upstream side of the filter. (Use a female-female Luer Lock adapter, if necessary.)
- Make sure that the outlet at the downstream side of the filter is open.
- Hold the syringe with the filter vertically with the downstream side of the filter facing upwards.
- Gently push the piston of the syringe downwards to displace the air at the upstream side with the wetting medium (tap water) until the resistance of the filter prevents further filling.
- Remove the syringe with the female-female adapter.

*Note: The adapter should be filled with water.*

#### 6.3.2 Filter testing

- Connect the filter to the filter integrity test device.

*Note: The upstream filter system has to be absolutely leakproof.*

- Choose the program according to table 1.
- Make sure that the downstream filter side is open.
- Mount the filter in a vertical position with the upstream side of the filter connected to the device facing up.
- Start the test program according to the corresponding setup and use the handling instruction of the device.

*Note: Vent the filtration system housing immediately after each test to avoid soiling of the integrity tester!*

- Vent the filter completely and disconnect the filter from the pressure outlet.

## 7 Example - water intrusion results for the hydrophobic filter

After the measurement is finished, the testing device will provide a printout summarizing the program parameters (shown in Table 2), the results of the test in a tabular and graphic form and whether the test was passed or not. In addition, the figures below serve as a reference to the resulting data.

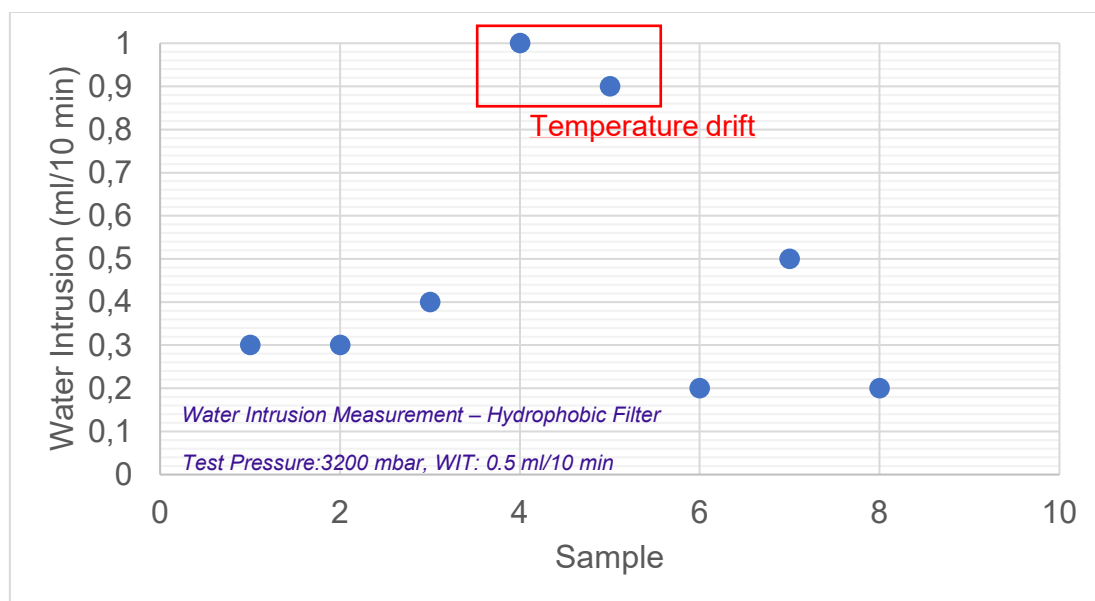


Figure 2 : Example - water intrusion test of hydrophobic filters